REMARKS

Applicant wishes to thank the Examiner for the careful consideration given this case. As examined, claims 1-17 were pending. New claims 18-21 have been added. Thus, claims 1-21 are presented for further consideration in light of the remarks below.

EXAMINER'S ACTION

The Office Action dated July 2, 2002, rejected claims 1-2, 4-7, 9-11, 13-15 and 17 under 35 U.S.C. § 112, first paragraph as containing subject matter, specifically the affinity ligand, which was not described in the specification in a way which reasonably conveys to one of ordinary skill in the art that the inventor had possession of the claimed invention at the time of filing.

The Office Action rejected claims 1-2, 4-5, 10-11, 13-15 and 17 under 35 U.S.C. § 102(e) as being anticipated by Hale et al. (U.S. Patent No. 6,120,766) and also by Aruffo et al. (U.S. Patent No. 6,051,228).

The Office Action rejected claims 1-17 under 35 U.S.C. § 103(a) as being unpatentable over Turk et al. (U.S. Patent No. 5,958,409) in view of Genain and Hauser and Anderson et al. (U.S. Patent No. 5,776,456).

The Office Action rejected claims 6-7 and 9 under 35 U.S.C. § 103(a) as being unpatentable over either Hale or Aruffo in view of Turk.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

As suggested by the Examiner, Applicant has amended claims 1-2, 4-7, 9-11, 13-15 and 17 to recite that the affinity ligand comprise an antibody. As the Examiner noted, the specification discloses examples of antibodies which bind to a B cell determinant and deplete B

cells, and therefore are supported by an adequate written description. To be sure, Applicant strongly traverses the conclusion that such an Amendment need be made to meet the written description requirement. Applicant reserves the chance to reintroduce these claims in a later Amendment or Application.

REJECTIONS UNDER 35 U.S.C. § 102(e)

The Office Action also rejected claims 1-2, 4-5, 10-11, 13-15 and 17 under 35 U.S.C. § 102(e) as being anticipated by Hale et al. (U.S. Patent No. 6,120,766). Hale discloses the antigen CDw52, which is an antigen present on all human lymphocytes and most monocytes. As such, antibodies to CDw52 bind to all lymphocytes and monocytes and lyse both B and T cells in vivo. (Hale, column 1, lines 35-42). In the present application, the B cell determinant to which the affinity ligand has binding affinity and avidity for is primarily expressed on B cells, with little or no expression by other immune cell subpopulations, except for dendritic cells as related to CD21. (See specification page 12).

As noted by the Office Action, the Federal Circuit held in *Bristol Meyers Squibb Co. v. Ben Venue Lab. Inc.*, that newly discovered uses of a known process are unpatentable because such results are inherent. *58 U.S.P.Q.2d 1508, 1514 (Fed. Cir. 2001)*. However, the Federal Circuit stated that the claimed process must be directed to the same steps and the same purpose as described by the prior art. *Id.* The present application does not entail the same steps as disclosed in Hale. The application involves the step of administering an affinity ligand which binds to a B cell determinant, which is expressed only by B cells. Hale discloses the steps of administering an antibody which binds indiscriminately to both B and T cells.

Furthermore, the purposes and claims of the present application are not the same as the teachings of the Hale. Hale teaches depletion of both B and T cells in an effort to treat MS. As amended, the claims call for a composition comprising an antibody binding to specific B cell determinants, among others.

The Office Action also rejected claims 1-2, 4-5, 10-11, 13-15 and 17 under 35 U.S.C. § 102(e) as being anticipated by Aruffo et al. (U.S. Patent No. 6,051,228). Aruffo discloses that CD40 is an antigen that is not expressed only by B cells, but rather is expressed by all antigen presenting cells, including dendritic cells, keratinocytes and monocytes, fibroblasts, eosinophils and activated T cells. (Aruffo, column 1, lines 17-25).

As noted above, in the present application the B cell determinant to which the affinity ligand has binding affinity and avidity for is primarily expressed on B cells, with little or no expression by other immune cell subpopulations, except for dendritic cells as related to CD21. (See specification page 12). Therefore, the present application does not entail the same steps as disclosed in Aruffo.

REJECTIONS UNDER 35 U.S.C. § 103(a)

The Office Action rejected claims 1-17 under 35 U.S.C. § 103(a) as being unpatentable over Turk et al. (U.S. Patent No. 5,958,409) in view of Genain and Hauser and Anderson et al. (U.S. Patent No. 5,776,456) and claims 6-7 and 9 under 35 U.S.C. § 103(a) as being unpatentable over either Hale or Aruffo in view of Turk.

A prima facie case of obviousness may be established when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." MPEP § 2141. When more than one reference is required to establish obviousness,

there must be "a teaching, suggestion or motivation to combine the references." *In re Rouffet 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998).* The burden may be satisfied "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).* The suggestion to combine must be shown to flow from the nature of the problem, the teachings of the pertinent references or from the ordinary knowledge of those skilled in the art that certain references are of special importance in a particular field. *In re Rouffet, 47 U.S.P.Q.2d at 1456.*

The Examiner must consider the claims in view of what the art teaches in determining obviousness, not what the Examiner speculates or believes. The rationale supporting an obviousness rejection must be based on common knowledge in the art or "well-known" prior art. This art must be capable of instant and unquestionable demonstration as being "well-known" in the art. MPEP § 2144.03.

As the Office points out, the marmoset model taught by Genain and Hauser is "novel," demonstrating that what is being taught by this model would not be common knowledge to one of ordinary skill in the art. Genain and Hauser teach that previous animal EAE models are not indicative of successful therapeutic treatment of MS in humans. However, the marmoset model has some of the same features as the previous animal EAE models. As such, the Genain and Hauser reference does not teach that its novel marmoset model is a reliable indicator for successful treatment of MS in humans, since it does employ some of the same features as the "unreliable" animal EAE models. The Office goes so far as to say that this novel model is the "standard animal model" for EAE, and relies on this reference as part of an obviousness rejection. The Office has not provided any references to support such a statement and has failed

to rebut the Applicant's evidence that the previous mouse EAE models were considered the standard experimental model for MS at the time of the invention.

Furthermore, Genain and Hauser teach away from the present application. Genain and Hauser teach that demyelination is an acute event in MS. Therefore, even if one of ordinary skill in the art "would immediately recognize in view of the teachings of Genain and Hauser that B cells, which were well known in the art to be the source of antibody," would cause antibody related demyelination, as the Office asserts (page 7, lines 24-25), one of ordinary skill in the art relying on Genain and Hauser would be taught away from using B cells as a therapeutic target for MS, since Genain and Hauser teach that MS involves only acute demyelination and therefore would not represent an effective therapeutic target for the treatment of MS or the progression of MS.

The Office notes that the Biozzi AB/H mice "were known in the art" to develop chronic-relapsing, rather than acute, EAE and more susceptible to EAE induction than Biozzi AB/L mice (page 7, line 41). The Office has not provided any support for such the factual assertion, nor any support showing that this factual assertion was known to one of ordinary skill in the art at the time of the invention. Such an assertion by the Office Action, based upon personal knowledge, must be supported by affidavit. 37 C.F.R. § 1.104(d)(2); MPEP § 2144.03.

Genain and Hauser do not teach, as the Office suggests, that one of ordinary skill in the art would find "identifying antibody produced by B cells as a primary target in MS" (page 8, lines 11-12). In the previous office action, the Applicant provided multiple references which show that B cells were not considered to be cells involved in the progression of MS. However, as stated above, even if the Genain and Hauser reference can be said to fairly suggest that antibodies produced by B cells are associated with demyelination in the marmoset model, there

is no support for the Office's assertion that this is knowledge generally known or available to one of ordinary skill in the art.

The Office Action also dismisses the references presented by the Applicant showing that the mouse model of EAE was the standard model for MS and simply states that "the Examiner does not agree" (page 8, line 46). The Office also asserts that the previous models are of chronic-sustained form of EAE, which is distinct from chronic-relapsing EAE, as used in the marmoset model (page 9, lines 2-4). The Office does not provide any references supporting any of these assertions. Applicant respectfully requests support in a reference of record or withdrawal of the rejections.

The Office states that reliance has not been made upon a particular antigen, specifically MOG. However, the Office relies on Genain and Hauser which are offered as teaching that production of a demyelinating MS lesion involves the interaction of encephalitogenic T cells, proinflammatory cytokines and pathogenic antibody. The pathogenic antibody taught in Genain and Hauser is against MOG. No other references are cited to show support for an antibody other than anti-MOG, in the involvement of demyelination. To the extent Genain and Hauser does suggest the involvement of antibody in MS, it only suggests the involvement of antibody to MOG.

Finally, the Office has failed to provide any objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would motivate one to combine the references. As such, a prima facie case of obviousness has not been set forth and the rejection should be withdrawn.

CONCLUSION

Applicant's attorney would like to thank the Examiner for the careful consideration given this case. In view of the remarks presented above it is believed that pending claims 1-21 are in condition for allowance and notice to such effect is respectfully requested. The Commissioner is authorized to charge any additional fees or credit any overpayments to Deposit Account No. 02-2051.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

1. (**Twice** Amended) A method for reducing a pro-multiple sclerosis (pro-MS) immune response in a**[n] human** individual, the method comprising administering to **[a] the** individual a composition, wherein the composition comprises an affinity ligand **comprising an antibody** which **[selectively]** binds to a B cell determinant, **wherein the B cell determinant is selected from the group consisting of CD19, CD 20, CD21, CD22, Lym-1, or a determinant expressed only by the B cells and not by immune cells other than B cells,** wherein **[the]** B cells targeted by the method and by the composition are nonmalignant B cells, and wherein the composition is administered in an amount effective to deplete B cells.

6. (**Twice** Amended) A site-directed method for reducing a pro-multiple sclerosis (pro-MS) immune response in a**[n] human** individual, the method comprising administering to **[a] the** individual a composition, wherein the composition comprises an affinity ligand **comprising an antibody** which **[selectively]** binds to a B cell determinant, **wherein the B cell determinant is selected from the group consisting of CD19, CD 20, CD21, CD22, Lym-1, or a determinant expressed only by the B cells and not by immune cells other than B cells,** wherein **[the]** B cells targeted by the method and by the composition are nonmalignant B cells, wherein the composition is delivered into an access that directly supplies central nervous tissue undergoing demyelination, and wherein the composition is administered in an amount effective to deplete B cells.

10. (**Twice** Amended) A method for reducing a pro-multiple sclerosis (pro-MS) immune response in **a[n] human** individual, the method comprising administering to **[a] the** individual a composition, wherein the composition comprises an affinity ligand **comprising an antibody** which **[selectively]** binds to a B cell determinant, **wherein the B cell determinant is selected from the group consisting of CD19, CD 20, CD21, CD22, Lym-1, or a determinant expressed only by the B cells and not by immune cells other than B cells,** wherein **[the]** B cells targeted by the method and by the composition are nonmalignant B cells, wherein the composition is administered intravenously, and wherein the composition is administered in an amount effective to deplete B cells.

14. (Twice Amended) A method for treating **a[n] human** individual having multiple sclerosis (MS) and a pro-MS immune response, or having a pro-MS immune response, the method comprising administering to **[a]** the individual a composition, wherein the composition comprises an affinity ligand **comprising an antibody** which **[selectively]** binds to a B cell determinant, **wherein the B cell determinant is selected from the group consisting of CD19, CD 20, CD21, CD22, Lym-1, or a determinant expressed only by the B cells and not by immune cells other than B cells,** wherein **[the]** B cells targeted by the method and by the composition are nonmalignant B cells, and wherein the composition is administered in an amount to effect a reduction in inflammation underlying clinical manifestations of MS.